Remarks

Claims 2-12 and 40 are pending in this application.

In response to the Office Action mailed **July 14, 2000,** the cited reference has been reviewed, and the rejections and objections made to the claims by the Examiner have been considered. The claims presently on file in the above-identified application are believed to be patentably distinguishable over the cited references, and therefore allowance of these claims is earnestly solicited.

In order to render the claims more clear and definite, and to emphasize the patentable novelty thereof, claims 2, 4, 6, 8, 11 and 12 have been amended, and claims 1 and 13-39 have been canceled without prejudice, and new claim 40 has been added.

Therefore, all claims presently on file in the subject application are in condition for immediate allowance, and such action is respectfully requested.

Rejection Under 35 U.S.C. §103(a)

Turning now to the Examiner's rejection of claims 1-12 under 35 U.S.C. §103(a), the Applicant has read and considered the Examiner's rejection and respectfully assert that the cited reference, United States Patent Number 5,292,632 issued to Bass et al March 8, 1994 (herein after "the Bass patent"), in fact teaches away from the present invention and, for additional reasons stated herein, does not render the present invention obvious. Moreover, the Applicant has deleted claim 1 and added new claim 40 of the present application to more clearly distinguish it over the cited reference.

The Examiner has stated that the Bass patent teaches adhesives that include globular and fibrous proteins including collagen and albumin. Moreover the examiner asserts that the Bass adhesives or sealants have cross-linking *moieties* and that the proteins can be modified using the application of energy and/or photons. Therefore, the differences between the prior art and the Applicant's high strength, biocompatible tissue adhesives, "if any" is the specific components and the ratio of ingredients. Consequently, it would have been obvious to one of ordinary skill in the art, with knowledge of the Bass patent, to make the Applicant's high strength, biocompatible tissue adhesives. The Applicant respectfully disagrees for the following reasons.

The adhesives disclosed in the Bass patent contain combinations of *untreated* proteins and can include other non-protein compounds including proteoglycans, saccharides, and polysaccharides. These compounds, in their *naturally occurring, unmodified form*, are premixed and applied to a wound. There is *no* cross-linking agent added (it is understood that cross-linkable moieties exist on complex unsaturated biomolecules including most proteins, however, there are no actual cross-linking agent added in the Bass invention). *After* the Bass adhesive is applied to a wound an *external* energy source such as electromagnetic, ultrasonic or thermal energy is used to "weld" the wound shut by activating the Bass tissue adhesive.

In contrast, the Applicants invention uses protein sub-components that are extensively modified using ultrasonic energy *before* compounding the adhesive. In fact, the ultrasonic treatment used in Applicant's invention can occur weeks, months or even years prior to adhesives' application to tissue and the application of ultrasonic energy is not used as a *post application activating agent.* Unlike the Applicant's tissue adhesive, the requirement of a post application activation step as taught by the Bass patent makes the Bass tissue adhesive unsuitable for sealing large vigorously bleeding tissue surfaces. Moreover, the need for a post application activation step using a mechanical source such as a laser, radio transmitter, x-ray machine or ultrasonic source significantly limits the utility of the Bass tissue adhesive. First, there are many regions of the body where such devices cannot reach including the interior of the heart and lungs. Secondly, the need to activate the adhesive post application renders it unsuitable for emergency room care or field use. The mere chance that a tissue adhesive may form a seal spontaneously in some cases (see column 5 line 47-48 of the Bass patent) renders it entirely unsuited for use in life threatening emergency situations.

Therefore, the Applicant, an emergency room physician and trauma surgeon, developed this present tissue sealant to fill a long felt need in the medical community. Specifically, to provide a high strength, biocompatible tissue adhesive capable of sealing massively bleeding large surface areas in emergency situations without the need for post application processing. Moreover, the present Applicant needed a sealant that had superior strength that could be applied to areas of the body, such as the lung, where bulking mechanical activating apparatuses such as

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those required to assure complete sealing with the tissue adhesive disclosed in the Bass patent, can not reach. (see the present application at page 8 lines 20-25).

As mentioned briefly above, the tissue adhesive disclosed in the Bass patent uses unprocessed proteins that are mixed and then *activated* after being applied to the tissue, and thus coagulated post application, using, among other techniques, ultrasonic energy. Therefore, it would be entirely unexpected that such an energy source could be used on similar material *prior* to mixing and application to tissues. The Bass patents' teachings would lead a person having ordinary skill in the art to conclude that ultrasonic energy causes the proteins used in the present invention to clot rendering them unsuitable as a *pre-application* tissue sealant ingredient. Consequently, it was entirely unexpected when the present Applicant developed a superior self-sealing tissue adhesive by individually pre-treating proteins similar to those disclosed in the Bass patent using ultra sonic energy prior to compounding the base adhesive or its application to tissues. Therefore, the Bass patent teaches away from the techniques and adhesive compounds described and now claimed by the present Applicant.

The Applicant has also developed a new cross-linking agent that is used in conjunction with the tissue adhesive of the present invention. This cross-linking agent is added immediately prior to application of the final adhesive composition. Once mixed the tissue adhesive requires no further processing and can be applied to tissues. The Bass patent neither teaches nor suggests the use of a cross-linker. Moreover the Bass patent would not motivate one of ordinary skill in the art to use a cross-linking compound. In fact, the only mention of cross-linking in the Bass patent is in reference to certain possible ingredients that may be used with the Bass tissue adhesive. In reference to these compounds, Bass teaches "...*cross-linked*...derivatives or subunits thereof" (see column 5 lines15-19 as an example). Here, the term cross-linked is used in the past tense suggesting that some cross-linking event has already occurred (note that no cross-linking step or compound is suggested). Therefore, it teaches away from further post compounding cross-linking immediately prior to application as taught by the present Applicant.

To reject a claimed invention as obvious, a patent examiner must establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in prior art cited

by the examiner or in knowledge generally available to one of ordinary skill in the art, to modify the reference, or combine the reference being relied on to reject the claimed invention. In the present case, the Applicant has shown that the teachings in the Bass reference in fact provides no such motivation and clearly teach away from the Applicant's tissue adhesives.

Secondly, there must be a reasonable expectation of success. In the present case, the Bass reference teaches the *post application* use of external energy to the final tissue adhesive composition. This would lead a person having ordinary skill in the art to conclude that the treatment of tissue adhesive ingredients with ultrasonic energy *prior to formulating the adhesive* would render the materials unusable for making a stable tissue adhesive. For example, it would be contra-intuitive to a chemist to expect that catalyzing a reaction *after all the reactants have been mixed* would give the same results as catalyzing the reactants individually *prior* to their mixing. Thus there would be no *reasonable* expectation of success when applying the Bass teachings to the present invention.

Finally, the prior art reference or combination of references must teach or suggest all of the requirements of the claimed invention. In the present case the Bass reference does not teach the use of a cross-linking agent, and it fact teaches away from the use of cross-linkers as previously described.

Thus, the cited reference does not disclose, nor suggest, the novel features of the present invention as claimed.

Conclusion

Claim 1 has been cancelled and new claim 40 has been added to clearly distinguish it from the Bass reference cited by the Examiner. Furthermore, the Applicant has proved detailed arguments that he asserts traverses the Examiner's rejection of claims 1-12 based on 35 U.S.C. §103(a). Therefore, the Applicant respectfully request reconsideration of claims 2-12 and new claim 40 as presently present and their swift allowance.

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Therefore, all claims presently on file in the subject application are in condition for immediate allowance, and such action is respectfully requested.

If it is felt for any reason that direct communication with Applicant's attorney would serve to advance prosecution of this case to finality, the Examiner is invited to call the undersigned attorney at the below listed telephone number.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 16-2230.

Respectfully submitted,

Dated: October 13, 2000

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